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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,311	06/21/2001	Liselotte Bjerre Knudsen	5515.214-US	6961

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,311	KNUDSEN ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92-123* is/are pending in the application.

4a) Of the above claim(s) *95,100-103 and 107-120* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92-94, 96-99, 104-106 and 121-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/312,177.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT FOR PRIORITY, IDS, SEQUENCE LISTING, AMENDMENT, RESPONSE TO RESTRICTION REQUIREMENT, STAUS OF THE APPLICATION AND CLAIMS

1. The preliminary amendment, the sequence listing, the Information Disclosure Statements (IDS) and Form PTO-1449, and the response to the restriction requirement filed 6/21/01, 9/11/03 and 4/12/04, respectively are acknowledged, entered and considered. This application is a Continuation of U.S. application Serial No. 09/312,177, filed 5/14/99, now abandoned, which is a Continuation of PCT/DK99/00086, filed 2/24/99 and claim priority under 35 U.S.C. § 119 for Danish application 0274/98, filed 2/27/98; and U.S. Provisional application 60/084,357, filed 5/5/98. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed in the file of parent application 09/312,177. In view of Applicant's request, the computer-readable form of the sequence listing of the parent application Serial No. 09/312,177, filed 5/14/99 has been transferred to the instant application Serial No. 09/886,311, filed 6/21/01 since the computer-readable form of the sequence listing of this application is identical to that in the parent application 09/312,177. Thus, in accordance with 37 C.F.R. 1.821(e), the computer-readable form of the sequence listing filed in the parent application has been entered and considered in the instant application.

In regard to IDS filed 6/21/01 (Paper No. 2), in view of Applicant's request, the references cited therewith in Form PTO-1449 are not provided in the instant

specification. However, as per Applicant's request, since the cited references were considered previously in the parent application Serial No. 09/312,177; pursuant to 37 CFR § 1.98(d), the references cited in Form PTO-1449 in this application have been considered and signed as requested by Applicant. Claims 92-123 are now pending in the application.

CLAIMS STAND WITHDRAWN WITHOUT TRAVERSE

2. Applicant's election of the species Arg^{33}, Leu^{20}, Gln^{34}, Lys^{18} (Nϵ-(γ-aminobutyrroyl(Nα-hexadecanoyl))) Exendin-4-(7-45)-NH_2 of claim 121 and claims 92-94, 96-99, 104-106 and 121-123 read thereon without traverse is noted. Therefore, claims 95, 100-103 and 107-120 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 4, filed1/22/4. Thus, the Office action is directed to the merits of claims 92-94, 96-99, 104-106 and 121-123 as per elected invention.

ABSTRACT OF THE INVENTION

3. The abstract of the invention is not descriptive. A new abstract is required that is clearly indicative of the invention to which the claims are directed.

CLAIMS REJECTION-35 U.S.C. § 112 FIRST PARAGRAPH

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 92-94, 96-99, 104-106 and 121-123 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a pharmaceutical composition containing exendin-3 or exendin-4, fragment thereof, or any combination thereof, for the treatment of diabetes mellitus, does not reasonably provide enablement for an exendin derivative having an amino acid sequence that differs from the amino acid sequence of exendin-3 or exendin-4 by the substitution of up to ten (claim 92) or up to six (claim 93) amino acid residues with any α-amino acid residue, wherein (a) one lipophilic substituent is attached to amino acid residues and (b) one of the lipophilic substituent is attached to an amino acid residue which is not the N-terminal or C-terminal amino acid residue (claims 92 and 93), to a pharmaceutical formulation comprising the composition of claim 92 as an active ingredient (claim 122) and to a method of treating insulin dependent or non-insulin dependent diabetes mellitus by administering a therapeutically effective amount of the composition of claim 92 (claim 123). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

The use of up to ten or six amino acid residues with any α-amino acid residue suggests that the amino acid sequence/residue intended to be modified by substitution

is either is not known or Applicant contemplates modification of an exendin derivative by substitution from 0 to 10 of amino acid residues in the peptide. Thus, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the amino acid residues identified by substitution of up to ten or six amino acid residues with any α-amino acid residue for the following reasons:

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspect of the protein is extremely complex. While it is known that amino acid substitution is generally possible in any given protein the positions within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of success are limited. Other positions in the sequence are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis and in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only relatively conservative substitutions or no substitutions (See e.g., Bowie et al., Science, Vol. 247, 1990, pp. 1306-1310, especially page 1306, col. 2, paragraph 2). Similarly, Houghten et al., teach the relative importance of position and individual amino acid residues in peptide antigen-antibody interactions. The reference shows that a protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Detailed examinations of other antibody-antigen systems are being carried out to establish the existence of general trends in peptide antigen recognition

patterns (See e.g., Houghten et al., Vaccines 86, Cold Spring Harbor Laboratory, 1986, pp. 21-25, especially page 24, last paragraph). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data (i.e., SEQ ID NOS: 1-3) to enable one of ordinary skill in the art to determine without undue experimentation by substitution of up to ten or up to six amino acid residues with any α- amino acid residue in the manner claimed in claims 92 and 93.

Further, Applicant has provided the sequences of exendin derivatives as disclosed in SEQ ID NOS: 1-3. From this Applicant is attempting to extrapolate to a broad diversity of exendin peptides bearing little relationship to exendin derivatives disclosed in the specification by claiming the substitution of up to ten or six amino acid residues with any α-amino acid residue. Thus, either in claim 92 or 93, any number of amino acids (at least from 0 to 10) can be replaced with any number ranging from 1-10 conservative or non-conservative substitution by insertion and/or deletion. The effects of this are unknown for the reasons discussed above, and as such, when this variable is added, the claimed invention becomes little more than conjecture. Moreover, without guidance, the changes which can be made in the peptide/protein structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessary and improperly, extensive and undue. See Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 927 F.2d, 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Furthermore, with respect to claims 122 and 123, there is no working example or data or evidence which shows the claimed exendin derivative is useful as a

pharmaceutical composition containing as an active ingredient a therapeutically effective amount of the exendin derivative administered to treat diabetes as claimed in claims 122 and 123. Although, there is protocol for preparation of pharmaceutical compositions as well as certain dosages as recited on pages 30-32 and 41-42, nevertheless, there is no evidence in the instant specification to use or administer the pharmaceutical composition in therapeutically effective amount as claimed, except for the demonstration of assays which show the efficacy of GLP-1 derivatives in their ability to stimulate formulation of cAMP in cell lines expressing the cloned human GLP-1 receptors *in vitro* as recited on page 50 in the instant specification disclosing the range of effective dosages of a pharmaceutical composition to be administered for the intended treatment of diabetes. Further, there are no sufficient data or evidence to substantiate such protocols of using pharmaceutical composition of claim 122 to be administered in a therapeutically effective amount to treat diabetic patients in the manner claimed in claim 123. Hence, the only support for the claimed pharmaceutical composition in the specification is Applicant's supposition of the invention as recited in the protocols. Furthermore, Applicant's claims are directed to a very large number of compounds by using specific therapeutically effective amount of a pharmaceutical composition, and there are no objective factual evidence in the specification showing that treatment has occurred using the specific therapeutically effective amount of a pharmaceutical composition claimed. Thus, one cannot administer specific effective amount of a pharmaceutical composition to treat diabetes in all situations without appropriate testing.

Moreover, the first paragraph of 35 U.S.C. 112 requires, inter alia, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation ..... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, the scope of the exendin derivative having an amino acid sequence that differs the amino acid sequences disclosed in the instant specification would involve substitution of the amino acid residues in the exendin-3 or -4 peptide with any number of amino acid residues ranging from 1-10 conservative or non-conservative. Hence, it would include those that have not been shown or taught to be useful or enabled by the disclosed method of making ad using the invention. Moreover, undue experimentation is necessary to determine if and under what conditions, the claimed

invention as broadly claimed is enabled, since any number of amino acid residues ranging from 1-10 are to be substituted with any amino acids identified as exendin-3 or -4 are contemplated and are encompassed as well as wide range of situations. The results desired appear to be highly dependent on all variables, the relationship of which is not clearly disclosed. Thus, without guidance through working example(s), one of ordinary skill in the art would not predict from the sequence data disclosed in the instant specification to substitute any number of amino acid residues with a range of at least 1-10 amino acids and be used as a pharmaceutical formulation by administering a therapeutically effective amount of said pharmaceutical formulation to treat diabetic patients in the manner claimed in the instant invention.

Therefore, applying the Wands factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims for the reasons given above. Thus, in view of the quantity of experimentation necessary, the lack of adequate guidance or working examples or data and the breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CLAIMS REJECTION-35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 92-94, 96-99, 104-106 and 121-123 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eng (U.S. Patent No. 5,424,286) taken with WO 96/29342.

Eng (U.S. Patent No. 5,424,286) teaches the use of a pharmaceutical composition containing exendin-3 or exendin-4, fragment thereof, or any combination thereof, for the treatment of diabetes mellitus (See e.g. abstract and summary of the invention) as directed to claims 92, 93, 122 and 123. On column 5, lines 20-32, the reference clearly states that the sequence of the invention also provide a means for identifying any specific mammalian analogs to the exendins. This can be accomplished by direct comparison of amino acid sequences, or by the translation of RNA or DNA sequences which may encode for the amino acid sequences of the invention. Thus,

clearly suggesting the use of designation analogue comprising derivatives wherein at least a total of up to 10 amino acid residues have been exchanged with any amino acid residue, which can be coded by the genetic code.

Eng (U.S. Patent No. 5,424,286) differs from claims 92-94, 96-99, 104-106 and 121-123 in not teaching peptide derivatives, which have been modified by attaching a lipophilic substituent, which is not C-terminal, or N-terminal amino acid residue. However, WO 96/29342 discloses a pharmaceutically active peptide hormone which has been modified by introducing a lipophilic substituent comprising from 8 to 40 carbon atoms in either the N-terminal or the C-terminal amino acid of the native peptide hormone or an analogue thereof (See e.g., page 2, lines 14-20) s directed to claims 94, 96 and 97. Further, the reference discloses the attachment of the lipophilic substituent to the parent peptide by means of a spacer, wherein the lipophilic substituent is the acyl group of a straight chain or branched fatty acid (See e.g., page 3, lines 1 to page 4, lines 14) as directed to claims 98, 99 and 104-106. Thus, alternately showing the attachment of lipophilic substituent, which is not C-terminal, or N-terminal amino acid residue. On page 4, lines 21 to 32, the reference clearly disclose a pharmaceutical formulation of the active peptide hormone with a pharmaceutically accepted carrier. Thus, the reference of WO 96/29342 discloses the introduction of attachment of a lipophilic group to at least one amino acid residue of a pharmaceutically active peptide hormone derivative including glucagon-like peptide (GLP-1).

Therefore, given the teachings of the secondary reference which teaches the attachment of a lipophilic group to at least one amino acid residue, one of ordinary skill

in the art would have been motivated to adapt the above scheme into the teachings of '286 patent of the primary reference of using exendin in a pharmaceutical composition for the intended purpose of treating diabetes mellitus because the method of introducing lipophilic substituent for the purpose of treating osteoporosis is known as taught by the secondary reference. Thus, one ordinary skill in the art would be motivated to employ an exendin derivative having at least one amino acid residue of the parent peptide attached to a lipophilic substituent for the purpose of introducing said exendin derivative to treat diabetes mellitus. Hence, the advantages of introducing lipophilic substituents in order to obtain protracted profile action is clearly disclosed in the secondary reference, moreover, such features are known or suggested in the art, and including such features with the use of exendin to treat diabetes mellitus as taught by '286 patent into the methods of the secondary reference of WO 96/29342, would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof for the intended purpose of introducing lipophilic substituents for uses of GLP-1 and exendin in a pharmaceutical composition for a method of treating diabetes mellitus.

Therefore, in view of the above, and in view of the combined teachings of the prior art; one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known method of introducing lipophilic substituents in order to obtain a protracted profile of action comprising administering an exendin derivative of pharmaceutical formulation for the intended purpose of treating

diabetes mellitus, absent of sufficient objective factual evidence or unexpected results to the contrary.

ALLOWABLE SUBJECT MATTER

6. Claim 121 would be allowable if written or amended to overcome the various rejections set forth on independent claim 92 in this Office action.

RASONS FOR INDICATION OF ALLOWABLE SUBJECT MATTER

7. The following is an Examiner's statement of reasons for the indication of allowable subject matter. The prior art of record does not disclose, teach or suggest the elected species of claim 121, namely the species Arg^{33}, Leu^{20}, Gln^{34}, Lys^{18} (Nϵ-(γ-aminobutyrroyl(Nα-hexadecanoyl))) Exendin-4-(7-45)-NH_2 in the manner claimed.

CONCLUSION AND FUTURE CORRESPONDENCE

8. Claims 92-94, 96-99, 104-106 and 121-123 are rejected and claims 95, 100-103 and 107-120 are not considered and are withdrawn as non-elected inventions.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The appropriate fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
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Mohamed/AAM

June 22, 2004.